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Specimen
T147
1624
12/15/04

HYDRAZIDE AND ALKOXYAMIDE ANGIOGENESIS INHIBITORS

Cross-Reference to Related Applications

This application is a continuation of U.S. Patent Application Ser. No. 09/833,917,
5 filed April 12, 2001, which claims priority to U.S. provisional patent application 60/197,262,
filed April 14, 2000.

Technical Field

The present invention relates to substituted hydrazides and N-alkoxyamides which are
10 useful for preventing angiogenesis, methods of making the compounds, compositions
containing the compounds, and methods of treatment using the compounds.

Background of the Invention

Angiogenesis, the fundamental process by which new blood vessels are formed, is
15 essential to a variety of normal body activities (such as reproduction, development and
wound repair). Although the process is not completely understood, it is believed to involve a
complex interplay of molecules which both stimulate and inhibit the growth of endothelial
cells, the primary cells of the capillary blood vessels. Under normal conditions, these
molecules appear to maintain the microvasculature in a quiescent state (i.e., one of no
20 capillary growth) for prolonged periods which may last for as long as weeks or in some cases,
decades. When necessary, however, (such as during wound repair), these same cells undergo
rapid proliferation and turnover within a 5 day period. (*The Journal of Biological Chemistry*,
267: 10931-10934 (1987), *Science*, 235: 442-447 (1987)).

Although angiogenesis is a highly regulated process under normal conditions, many
25 diseases (characterized as "angiogenic diseases") are driven by persistent unregulated
angiogenesis. For example, ocular angiogenesis has been implicated as the most common
cause of blindness and dominates approximately 20 eye diseases. In certain existing
conditions such as arthritis, newly formed capillary blood vessels invade the joints and
destroy cartilage. In diabetes, new capillaries formed in the retina invade the vitreous, bleed,
30 and cause blindness. Growth and metastasis of solid tumors are also angiogenesis-dependent
(*Cancer Research*, 46: 467-473 (1986), *Journal of the National Cancer Institute*, 82: 4-6
(1989)).

Because the pivotal role played by angiogenesis in tumor formation, metastasis, other disease
conditions such as arthritis, inflammation, macular degeneration of age, and diabetic
35 retinopathy, agents which inhibit angiogenesis have been the subject of active current
research for their clinical potential.

In *Proc. Natl. Acad. Sci. USA*, 94: 6099-6103 (1997) and *Chemistry and Biology*,
4(6): 461-471 (1997) it is reported that both AGM-1470 and ovalicin, a sesquiterpene isolated